

## **CLAIM AMENDMENTS:**

1. (currently amended) A method for biotechnologically producing valuable products in which a medium is fed from an upstream feed receptacle (2, 3, 4) to a bioreactor (1) by a feed line (7, 9, 11) and a feed pump (8, 10, 12) and subjected to a fermentation process and in which the valuable product is harvested, as filtered permeate in a first downstream harvest receptacle (16) and/or as concentrated retentate in a second harvest receptacle (18),

said method further comprising a filtration step comprising conveying product from the bioreactor to a single downstream cross-flow filtration unit which is (5) connected to said bioreactor (1) by a conveying line (13) and a retentate line (17), and wherein said downstream cross-flow filtration unit (5) is further connected to said first downstream harvest receptacle (16) by a permeate line (15),

and wherein residues from the filtration step are re-supplied by said retentate line to the bioreactor until harvesting as retentate ~~by said retentate line~~ (17), wherein said retentate ~~can be~~ is removed from the bioreactor by a harvest line (19) connected to said second harvest receptacle (18) for storing a cell-contaminated harvest of the retentate,

said method further characterized in that, in addition to the medium, other substances can be fed to the bioreactor (1) in a controlled manner,

and wherein said concentrated retentate and said permeate are ~~can be~~ harvested in a controlled manner and wherein said fermentation process and the filtration are regulated in an integrated system, by a control unit (6),

and wherein cell concentration is measured and regulated in said bioreactor (1) by said control unit (6) which further comprises an analytical system (27) which

measures the cell concentration using a sensor (28) which is arranged in the bioreactor (1),

wherein said sensor (28) is connected to an analyzer (41) which is connected to a first regulator (42) which compares the actual value of cell concentrate with the desired value of a first reference operator (43),

and wherein said analytical system (27) regulates the cell concentration in the bioreactor (1) by controlling a harvest pump (20) which is located upstream of the second harvest receptacle (18),

and wherein in response to a signal said harvest pump (20) moves said concentrated retentate cell concentration from said bioreactor (1) to said second harvest receptacle (18); and

wherein said method further comprises a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1),

wherein said second regulator (44) compares the weight of said bioreactor (1) with a desired weight stored in a second reference operator (45),

and based on the comparison of the measured weight and the desired weight said second regulator (44) sends a control signal to an upstream feed pump (8), which sends medium to the bioreactor (1) from said upstream feed receptacle (2).

2. (original) The method as claimed in claim 1, characterized in that the integrated system can be cleaned and sterilized in situ, with this being controlled by the control unit (6).

3. (previously presented) The method as claimed in claim 1, characterized in that recombinant proteins are produced as valuable products, with the permeate yielding a cell-free harvest and the retentate yielding a cell-contaminated harvest.

4. (previously presented) The method as claimed in claim 1, characterized in that the method proceeds while being conducted in a sequential and integrated manner.

5. (previously presented) The method as claimed in claim 3, characterized in that, in a batch phase (29), cells which are supplied to the bioreactor (1) adapt to the medium and, in a subsequent fed batch phase (30), the cells are propagated at a constant growth rate by means of feeding.

6. (previously presented) The method as claimed in claim 3 characterized in that, in a production phase (31), the induction of product formation, and the actual production of the recombinant proteins, take place by means of adding an inducing substance.

7. (original) The method as claimed in claim 6, characterized in that the concentration of the inducing substance is measured by way of flow diffusion analysis and regulated by feeding from a second feed receptacle (3).

8. (previously presented) The method as claimed in claim 4, characterized in that, in a product harvesting phase (32), a part of the bioreactor (1) is harvested cell-free.

9. (original) The method as claimed in claim 8, characterized in that, in a cell harvesting phase (33), cell mass in the retentate is harvested and this is followed by a medium refreshing phase (34) involving the feeding of medium (35).

10. (original) The method as claimed in claim 9, characterized in that, after the medium refreshing phase (34), the cyclic process, in which, except in the product harvest, only the retentate stream, and not the permeate stream, is to flow, begins once again with the production phase (31).

11. (previously presented) The method as claimed in claim 3, characterized in that the recombinant proteins are produced using the yeast *Pichia pastoris*.

12. (original) The method as claimed in claim 11, characterized in that methanol (36) is added, as inducing substance, to the medium (35) in the bioreactor (1) in order to induce the sequences of the cell protein.

13. (original) The method as claimed in claim 12, characterized in that the methanol concentration is maintained at a constant level.

14. (previously presented) The method as claimed in claim 11, characterized in that glycerol (37) is fed in, in the fed batch phase (30) and/or in the production phase (31), for increasing production.

15. (previously presented) The method as claimed in claim 1, characterized in that the method proceeds while being conducted in a continuous and integrated manner.

16. (original) The method as claimed in claim 15, characterized in that the production phase (31), the product harvesting phase (32) and the cell harvesting phase (33) proceed in parallel.

17. (currently amended) A device for biotechnologically producing valuable products, comprising a bioreactor (1) having an upstream first feed receptacle (2) for a medium and a single downstream cross-flow filtration unit (5) connected by a

permeate line (15) to a first harvest receptacle (16) and wherein said single downstream cross-flow filtration unit (5) is connected to a retentate line (17) connected to said bioreactor (1),

wherein at least one second feed receptacle (3) containing an inducing substance is located upstream of the bioreactor (1),

and wherein a second harvest receptacle (18) for a cell-contaminated harvest of the retentate is connected to said bioreactor (1) by way of a harvest line (19),

and wherein a control unit (6) measures and regulates the fermentation and filtration process,

and wherein cell concentration is measured in said bioreactor (1) by said control unit (6) which further comprises an analytical system (27) which measures the cell concentration using a sensor (28) within the bioreactor (1),

wherein said sensor (28) is connected to an analyzer (41) which is connected to a first regulator (42) which compares the actual value of cell concentrate with the desired value of a first reference operator (43),

and wherein said analytical system (27) regulates the cell concentration in the bioreactor (1) by controlling a harvest pump (20) located upstream of the second harvest receptacle (18),

and wherein said harvest pump (20) is operable to move ~~moves~~ said cell concentration ~~concentrated retentate~~ from said bioreactor (1) to said second harvest receptacle (18); and

wherein said device further comprises a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1),

wherein said second regulator (44) is connected to a second reference operator (45) which contains stored weight values for the bioreactor (1),

and wherein said second regulator (44) is connected to an upstream feed pump (8), which is connected to said upstream first feed receptacle (2).

18. (original) The device as claimed in claim 17, characterized in that, for the purpose of measuring the concentration of the inducing substance in the bioreactor (1), the control unit (6) possesses an analytical system (24) which measures the concentration of the inducing substance by way of a sensor which is arranged in the bioreactor (1) and regulates the concentration of inducing substance in the bioreactor (1) by controlling a second feed pump (9) which is located upstream of the second feed receptacle (3).

19. (original) The device as claimed in claim 18, characterized in that the analytical system (24) is in the form of a flow diffusion analysis (FDA) system.

Claims 20 and 21. (cancelled).